Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

journal homepage: www.elsevier.com/locate/preghy

Effects of postpartum uterine curettage in the recovery from Preeclampsia/Eclampsia. A randomized, controlled trial

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ARTICLE INFO

Article history:
Received 11 February 2017
Received in revised form 10 April 2017
Accepted 4 June 2017
Available online xxxx
Synopsis: Postpartum uterine curettage is not useful in reducing hospitalization time or in improving the clinical evolution of the patient with preeclampsia/eclampsia.

Keywords:
Postpartum uterine curettage
Preeclampsia
Eclampsia

ABSTRACT

Objective: To evaluate if postpartum uterine curettage improved the clinical and laboratory parameters in patients with preeclampsia or eclampsia.
Methods: A total of 442 patients with preeclampsia/eclampsia were randomized to postpartum curettage (223) or no procedure (219). Systolic and diastolic blood pressure were recorded and analyzed at hours 6, 12, 24 and 48. Also, several laboratory values and diuresis were evaluated.
Results: No statistical differences were found between groups (curettage vs. no procedure) in regards to systolic [155.74(15.43) vs. 156.81(15.58)] and/or diastolic blood pressure [101.51(11.44) vs. 101.70 (11.20)] before and after the allocated procedure, starting at hour 6 [SBP: 134.19(13.11) vs. 136.65 (15.36); DBP: 87.20(9.42) vs. 88.57(10.98)] and up to 48 h after delivery [SBP: 126.59(15.54) vs. 128.21(13.85); DBP: 81.86(9.92) vs. 81.67(11.33)]. No statistical differences between groups were found in the rate of recovery of laboratory values, as well as in the need for additional antihypertensive medications in the postpartum period. These results applied to patients with severe preeclampsia (210 patients in both arms) and eclampsia (13 vs. 9). There were no cases of postpartum eclampsia or acute renal failure after delivery in any of the groups.
Conclusion: To perform a postpartum uterine curettage does not present an advantage in the patient with preeclampsia/eclampsia. The procedure dos not improve clinical or laboratory values.

1. Introduction

Hypertensive disorders of pregnancy are one of the main causes of maternal morbidity and mortality around the world. The estimated global incidence of preeclampsia is 2.16% of all pregnancies, with great disparities between countries. It can be as low as 0.20% and as high as 6.71% [1] but annually more than 50 000 maternal deaths worldwide are due to preeclampsia/eclampsia [2].

It has been proposed that the clinical signs of preeclampsia in the mother are due to endothelial dysfunction, a direct consequence of abnormal placentation [3] which may lead to placental ischemia. This process causes the release of placental products or can induce oxidative stress at the placental level, both causing damage to the maternal endothelium [4].

Since delivery is the only known treatment for preeclampsia, some researchers suggested that the complete removal of all trophoblastic tissue is necessary for the resolution of the condition and reducing the risk of related complications. However, many of these studies were either too small (sample size) or were not controlled. Only two randomized controlled trials (Adarsh et al. [5] and Ragab et al. [6]) had an appropriate sample size, but the first one was restricted to patients with eclampsia. The study done by Ragab et al. is the largest one to date, but reported a rate of postpartum eclampsia higher than the one described in worldwide literature. In a recent research paper published in JAMA, Ebrahim et al. [7] analyzed studies that completed a reanalysis of individual patient data from previously published RCTs addressing the same hypothesis as the original RCT. It was their conclusion that more than 35% "of published reanalyses led to changes in findings that implied conclusions different from those of the original article".

Considering that uterine curettage is an invasive procedure with substantial risks (infection and uterine perforation) and that available evidence supporting its use in patients with preeclampsia (a population with its own intrinsic risks) is limited but still performed in many countries, we decided to reexamine the hypothesis that a postpartum uterine curettage immediately after delivery to remove all trophoblastic and decidual tissue would have an impact

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http://dx.doi.org/10.1016/j.preghy.2017.06.001
2210-7789/

in improving the outcomes and accelerating the resolution of preeclampsia/eclampsia syndrome in the puerperium.

2. Materials and methods

We conducted a prospective, randomized controlled trial between October 2015 and October 2016. Women with singleton pregnancies, 24 or more weeks of gestation, admitted to our hospital for labor/delivery and a clinical diagnosis of severe preeclampsia or eclampsia were eligible to participate. Exclusion criteria were a known history of seizures or of cardiovascular, hepatic or renal disease. Once informed consent was obtained, the patient was randomized to either a postpartum uterine curettage immediately after delivery or routine management, independent of the form of termination (vaginal or cesarean). All patients were in stable condition (no evidence of maternal hemodynamic instability or fetal distress) before randomization, and their management afterwards followed the standards accepted in our country and established in the national guidelines for the management of hypertensive disorders of pregnancy (severe preeclampsia/eclampsia). All patients were evaluated hourly and received magnesium sulphate before delivery to prevent eclampsia and for a minimum of 12 h postpartum (24 h in the case of eclampsia). For hypertensive crisis the first drug used was labetalol (20 mg IV every 10 min to a maximum total dose of 300 mg) and the need for additional treatment or a continuous administration of oral antihypertensive drugs in the puerperium was determined by the attending physician on a clinical response basis.

For the sample size calculation, we decided to use the study done by Ragab et al. Their main outcome was mean arterial blood pressure and they described a shorter amount of time required to reach a mean arterial pressure of 105 mmHg or less in the curettage group (40 ± 3.15 h) than in the control group (86 ± 5.34 h). With an α error rate of 5% and a power of 80%, the calculated sample size was 438 (219 per group). A total of 482 patients (241 per group) were deemed necessary to account for drop-outs or other problems during follow-up.

The randomization protocol required that when the patient arrived at the labor and delivery unit or the operating room, a designated member of the staff had to open the sealed, opaque envelope, containing a computer generated code that randomized the patient into one of two groups (curettage or no procedure). After delivery, active management of the third stage of labor was performed in both groups. The only difference was that in the curettage group, after extraction of the placenta, an immediate postpartum curettage was performed using a #14 or #16 sharp curette. The cervix was visualized and a tenaculum used to grasp the anterior cervix. With a gentle technique, to avoid perforation, the curette was inserted until the fundus of the uterus was located and in a systematic fashion the entire cavity curetted, going from one uterine horn to the other over the fundus and including both anterior and posterior walls. The end point of the procedure was the "uterine cry" (the detection of a scratching sensation or sound), which represents the sharp curette running over the myometrium. Intravenous tramadol was used for analgesia five minutes before the procedure in vaginal deliveries. In case of a cesarean section, curettage was done in the operating room before suturing the uterus, and included both lower and upper uterine segments. The vital signs were monitored the entire time in both settings.

Standard laboratory assessments (hemoglobin, hematocrit, platelets, renal and liver function tests) were performed in every patient on admission and at hours 6, 12, 24 and 48 postpartum. Vital signs and diuresis were measured every hour while magnesium sulphate was being used and then at the same time intervals as mentioned before, afterwards.

The primary outcome of the study was to evaluate the systolic and diastolic blood pressure values at hours 6, 12, 24 and 48 postpartum. Secondary outcomes were laboratory results at hours 6, 12, 24 and 48 postpartum and the rate of seizures after birth.

Statistical analysis was performed using Epi Info version 7.0 (Centers for Disease Control and Prevention, Atlanta GA). Differences in continuous variables were analyzed using the Mann-Whitney *U* test and non-continuous variables were analyzed using the chi-square test. Statistical significance was set at $p < 0.05$. The study was approved by the Saint Thomas Hospital's Ethics Review Committee (Approval Number: 1098-2015/CIDI/HST) and registered in a public database (ClinicalTrials.gov – NCT03028194).

3. Results

A total of 595 patients (severe preeclampsia: 550/eclampsia: 45) were screened, but 115 refused to participate or did not fulfilled the inclusion criteria. Out of the 480 patients randomized, 38 were excluded from the final analysis (curettage was required for persistent postpartum bleeding in two cases and protocol was breached in other two. The other 34 were excluded due to incomplete information of the variables under study). Therefore, our sample was made of 442 patients (curettage: 223/no procedure: 219), in accord with our initial calculation (Fig. 1).

The baselines characteristics of both groups were similar (Table 1) with respect to maternal age, gestational age, parity, blood pressure (systolic and diastolic), rate of seizures prepartum, use of antihypertensive drugs prepartum, rate of cesarean sections and laboratory results.

The analysis of the primary outcome (systolic and diastolic blood pressure) showed (Table 2) that in both arms of the study (curettage vs. no procedure) after delivery there was a decreased in initial SBP [155.74(15.43) vs. 156.81(15.58)] and diastolic blood pressure [101.51(11.44) vs. 101.70(11.20)] starting at hour 6 [SBP: 134.19(13.11) vs. 136.65(15.36); DBP: 87.20(9.42) vs. 88.57 (10.98)], but the difference was not statistically significant between groups. This tendency was evident in the following evaluations of both systolic pressure [12 h: 129.30(12.99) vs. 130.91 (14.71) $p = 0.19$; 24 h: 125.02(15.37) vs. 126.94(15.05) $p = 0.40$; 48 h: 126.59(15.54) vs. 128.21(13.85) $p = 0.65$] and diastolic pressure [12 h: 83.54(9.59) vs. 84.59(10.21) $p = 0.31$; 24 h: 81.61(8.67) vs. 82.58(12.40) $p = 0.38$; 48 h: 81.86(9.92) vs. 81.67(11.33) $p = 0.66$].

There were no statistical differences in laboratory values at the same time intervals (Table 3). This secondary outcome included platelet count, creatinine, uric acid, blood urea nitrogen, total bilirubin, liver enzymes (AST-Alanine transaminase/AST-Aspartate transaminase) and lactate deshydrogenase, Also, there was no difference in the average level of diuresis up to the point where magnesium sulphate was omitted and Foley catheter retired. We had no cases of postpartum eclampsia, acute kidney failure or injury to pelvic organs due to the procedure or the need to reinstate the magnesium sulphate protocol for hypertensive crisis.

Although many patients required the use of antihypertensive medications in their puerperium, there was no statistical difference between groups. Of the 223 patients in the curettage group, 93.27% (208) required antihypertensive drugs, while 95.43% (209 patients out of 219) of the patients in the "no procedure" group required medications to control their blood pressure after delivery ($p = 0.17$). In most cases, the blood pressure was controlled using oral hydralazine (50 mg orally every 8 h), amlodipine (5 mg every day) or slow release nifedipine (30 mg every day), but as we mentioned before, the drug of choice was left in the hands of the

Please cite this article in press as: G. Mc Lean et al., Effects of postpartum uterine curettage in the recovery from Preeclampsia/Eclampsia. A randomized, controlled trial, Preg. Hyper: An Int. J. Women's Card. Health (2017), http://dx.doi.org/10.1016/j.preghy.2017.06.001